600. *Synthesis of Dihydropsoralidin, Isopsoralidin, and Their Methyl Ethers.**

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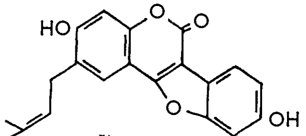
Syntheses of dihydropsoralidin (II) and isopsoralidin (III) and their methyl ethers are described.

Psoralidin, isolated[1] from the seeds of *Psoralea corylifolia* Linn., has recently been assigned[2] the structure (I), on the basis of degradations and ultraviolet and infrared spectra. In view of its close structural relation to coumestrol,[3] an œstrogen of forage,[4] we were interested to effect a practical synthesis of this and related compounds, at the same time confirming its structure. Psoralidin itself being labile towards acid, a synthesis of dihydropsoralidin (II; R = H) and isopsoralidin (III; R = H), the product of acid-catalysed cyclisation, was first undertaken.



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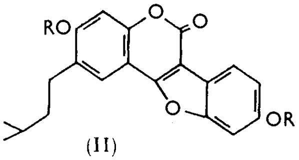

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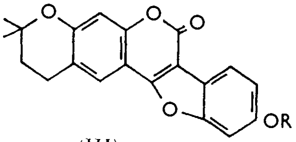

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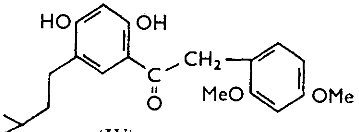

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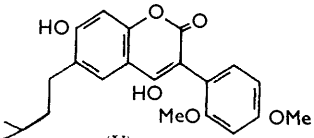

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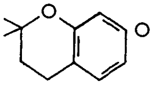

(VI)

2,4-Dihydroxy-5-isopentylphenyl 2,4-dimethoxybenzyl ketone (IV), prepared by Hoesch reaction of 2,4-dimethoxybenzyl cyanide[5] with 4-isopentylresorcinol,[6] was condensed with ethyl chloroformate in presence of anhydrous potassium carbonate.[7] The product, on treatment with alkali and then with acid, afforded 4,7-dihydroxy-6-isopentyl-3-(2,4-dimethoxyphenyl)coumarin (V) in good yield. This underwent demethylation with simultaneous ring-closure on being heated with aniline hydrochloride,[8] furnishing 6′,7-dihydroxy-6-isopentylbenzofurano[3′,2′:3,4]coumarin (II; R = H) which formed a diacetate and a dimethyl ether (II; R = Me). This ether was identical with that obtained from dihydropsoralidin (mixed m. p. and identical ultraviolet and infrared spectra).

7-Hydroxy-2,2-dimethylchroman[9] (VI) which served as the starting material for the synthesis of isopsoralidin was obtained by the action of an excess of methylmagnesium iodide on dihydroumbelliferone, in about 50% yield. An alternative route from methyl β-(2,4-dimethoxyphenyl)propionate by successive treatment with methylmagnesium iodide and a mixture of acetic acid and hydrobromic acid[10] did not succeed, the demethylation

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* For a preliminary account see *J. Sci. Ind. Res., India,* 1962, **21** *B,* 51, 148.

[1] Chakravarti, Bose, and Siddiqui, *J. Sci. Ind. Res., India,* 1948, **7***B*, 24.

[2] Khastgir, Duttagupta, and Sengupta, *Tetrahedron,* 1961, **14**, 275; Duttagupta, Khastgir, and Sengupta, *Chem. and Ind.,* 1960, **48**, 937.

[3] Bickoff, Lyman, Livingston, and Booth, *J. Amer. Chem. Soc.,* 1958, **80**, 3969.

[4] Bickoff, Livingston, and Booth, *Arch. Biochem. Biophys.,* 1960, **88**, 262.

[5] Mitter and Maitra, *J. Indian Chem. Soc.,* 1936, **13**, 236.

[6] Dohme, Cox, and Miller, *J. Amer. Chem. Soc.,* 1926, **48**, 1688.

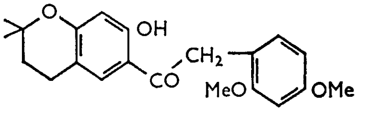
[7] Gilbert, McGookin, and Robertson, *J.,* 1957, 3740.

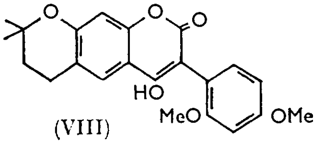
[8] Schoenberg and Aziz, *J. Amer. Chem. Soc.,* 1953, **75**, 3265.

[9] Späth and Mocnik, *Ber.,* 1937, **70**, 2276; Bridge, Crocker, Cubin, and Robertson, *J.,* 1937, 1530.

[10] John and Günther, *Ber.,* 1939, **72**, 1649.

stage leading to intractable low-boiling products.[11] Hoesch condensation of 2,4-dimethoxybenzyl cyanide with 7-hydroxy-2,2-dimethylchroman (VI) furnished 2,4-dimethoxybenzyl 7-hydroxy-2,2-dimethylchroman-6-yl ketone (VII) which was converted into the


(VII)


(VIII)

4-hydroxycoumarin derivative (VIII) and thence into isopsoralidin (III; R = H) by methods already stated. The synthetic isopsoralidin afforded a monoacetate and a monomethyl ether identical with those derived from the natural product.[2]

EXPERIMENTAL

M. p.s are corrected. Ultraviolet absorption spectra were recorded for ethanolic solutions on a Beckman spectrophotometer. Light petroleum refers to the fraction, b. p. 40—60°.

4-Isopentylresorcinol.—4-Isopentylresorcinol, m. p. 68°, was prepared according to the method of Dohme, Cox, and Miller [6] by condensing isovaleric acid with resorcinol in presence of zinc chloride and Clemmensen reduction of the resulting 2,4-dihydroxyisovalerophenone. The latter had m. p. 73° (Found: C, 68·3; H, 7·0. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·2%) and gave a dinitrophenylhydrazone, m. p. 234° (Found: C, 54·2; H, 4·9; N, 14·9. $C_{17}H_{18}N_4O_6$ requires C, 54·5; H, 4·8; N, 15·0%). Dohme *et al.*[6] report m. p.s 108—110° and 61—62·5° for the ketone and 4-isopentylresorcinol, respectively. While no explanation for the discrepancy in the m. p. of the ketone was apparent, the correct elemental analyses of the ketone and its derivatives left little doubt about the present compounds. Other workers [12] do not report the m. p.

2,4-Dihydroxy-5-isopentylphenyl 2,4-Dimethoxybenzyl Ketone (IV).—Into an ice-cold solution of 4-isopentylresorcinol (8·0 g.) and 2,4-dimethoxybenzyl cyanide (7·4 g.) in dry ether (100 ml.) containing freshly fused zinc chloride (3·2 g.) was passed a slow stream of dry hydrogen chloride for 6 hr. The red solution was kept at 0° for 4 days and then diluted with ether (100 ml.). The ketimine hydrochloride thus separated was collected, washed with a little ether, and refluxed with water (200 ml.) for 2 hr. *2,4-Dihydroxy-5-isopentylphenyl 2,4-dimethoxybenzyl ketone* (IV), obtained on cooling, crystallised from aqueous ethanol in needles (4·2 g.), m. p. 110° (Found: C, 70·3; H, 7·4. $C_{21}H_{26}O_5$ requires C, 70·4; H, 7·3%).

4,7-Dihydroxy-6-isopentyl-3-(2,4-dimethoxyphenyl)coumarin (V).—A mixture of the above ketone (1·5 g.), ethyl chloroformate (1·5 ml.), anhydrous potassium carbonate (6 g.), and dry acetone (45 ml.) was refluxed on the water-bath for 5 hr. Acetone was partly removed by the water-pump and the residue diluted with water (90 ml.) and acidified with hydrochloric acid. The crude solid (1·6 g.), m. p. 140—145°, was warmed in aqueous N-sodium hydroxide (100 ml.) on a water-bath for 1 hr. and the mixture was filtered, and acidified. The gelatinous precipitate was collected and crystallised from ethanol in stout prisms (1·3 g.), m. p. 186° (Found: C, 68·6; H, 6·5. $C_{20}H_{24}O_6$ requires C, 68·8; H, 6·3%). The present method of hydrolysis was superior to that employed by Emerson and Bickoff.[13]

6′,7-Dihydroxy-6-isopentylbenzofurano[3′,2′:3,4]*coumarin* (*Dihydropsoralidin*) (II; R = H).—The preceding coumarin (V) (0·7 g.) and aniline hydrochloride (2 g.) were heated at 210—220° for 4 hr. in a carbon dioxide atmosphere. The brown mixture was leached with water, and the organic matter repeatedly extracted with ether. The dried (Na_2SO_4) ethereal layer was evaporated and the residue (0·6 g.) refluxed with acetone (50 ml.), anhydrous potassium carbonate (8 g.), and methyl iodide (15 ml.) during 10 hr. After removal of acetone, the residue was diluted with water, and the solid collected and washed free from the brown material by a little ethanol. The dimethyl ether (II; R = Me) obtained as almost white solid (0·5 g.), m. p.

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[11] Cf. Smith, Ungnade, Opie, Prichard, Carlin, and Kaiser, *J. Org. Chem.*, 1939, **4**, 323.

[12] Cox, *Rec. Trav. chim.*, 1931, **50**, 848; Chudgar and Shah, *J. Univ. Bombay, India*, 1944, **13**, Part 3, 18; *Chem. Abs.*, 1945, **39**, 4078.

[13] Emerson and Bickoff, *J. Amer. Chem. Soc.*, 1958, **80**, 4381.

184—186°, crystallised from benzene–light petroleum and then from acetic acid–methanol in white plates (0·25 g.), m. p. 193—194°, identical with authentic dihydropsoralidin dimethyl ether (Found: C, 71·7; H, 6·4. Calc. for $C_{22}H_{22}O_5$: C, 72·1; H, 6·1%), $\lambda_{max.}$ 209, 243, 304, and 344 mμ (ε 41,200, 25,130, 8150, and 30,290, respectively). The infrared spectra of the synthetic and the natural methyl ether were identical. Dihydropsoralidin (II; R = H) obtained by demethylating the above methyl ether with aniline hydrochloride crystallised from methanol in light yellow plates, m. p. 295—297° (Found: C, 70·6; H, 5·3. Calc. for $C_{20}H_{18}O_5$: C, 71·0; H, 5·4%), $\lambda_{max.}$ 244, 305, and 348 mμ (ε 23,820, 9850, and 27,900, respectively). Khastgir *et al.*[2] report m. p. 275—277°. The free phenol (II; R = H) decomposes on storage and a direct comparison was not possible in absence of a pure sample from the natural source. The *diacetate* crystallised from ethanol in needles, m. p. 245—247° (Found: C, 67·6; H, 5·4. $C_{24}H_{22}O_7$ requires C, 68·2; H, 5·2%).

β-(2,4-*Dihydroxyphenyl*)*propionic Acid*.—β-(2,4-Dihydroxyphenyl)propionic acid, m. p. 165°, was prepared in quantity by cyanoethylation of resorcinol in presence of zinc chloride according to the procedure of Langley and Adams.[14] The derived dimethyl ether obtained by use of dimethyl sulphate and sodium hydroxide had m. p. 103° and was also prepared as follows:

2,4-Dimethoxybenzaldehyde, m. p. 70° (12 g.), malonic acid (17 g.), pyridine (25 ml.), and piperidine (1 ml.) were heated at 80° for 1 hr. and then for 2 hr. at 100° and for 30 min. under reflux.[15] 2,4-Dimethoxycinnamic acid (12 g., 80%), m. p. 188—190° (Found: C, 63·4; H, 5·9. Calc. for $C_{11}H_{12}O_4$: C, 63·5; H, 5·8%), thus obtained was dissolved in 2N-potassium carbonate (10% excess) and shaken under hydrogen in presence of 30% palladium–charcoal[16] (0·2 g.), to give β-(2,4-dimethoxyphenyl)propionic acid, m. p. 103—103·5° (lit.,[14] 102·5—103·5°). The methyl ester, b. p. 160°/10 mm., was prepared by refluxing the acid with methanolic sulphuric acid.

Lactone of β-(2,4-*Dihydroxyphenyl*)*propionic Acid* (*Dihydroumbelliferone*).—β-(2,4-Dihydroxyphenyl)propionic acid was slowly distilled from an air-bath under a vacuum, the lactone, b. p. 160—70°/3 mm., m. p. 130—132°, being obtained in about 40% yield and crystallised from toluene in white flakes.

7-*Hydroxy*-2,2-*dimethylchroman* (VI).—An attempt to prepare the chroman (VI) by the action of an excess of methylmagnesium iodide on methyl β-(2,4-dimethoxyphenyl)propionate and demethylation of the resultant alcohol (13 g.) by a refluxing mixture of acetic acid (50 ml.) and hydrobromic acid (15 ml.; *d* 1·49) under carbon dioxide for 2 hr. led to a product (4·2 g.), b. p. 130—160°/5 mm. This was insoluble in alkali and did not give a test for phenols.

7-Hydroxy-2,2-dimethylchroman was prepared by a slightly modified procedure of Späth and Mocnik[9] as follows: To a Grignard reagent prepared from magnesium (4·8 g.), methyl iodide (14·4 ml.), and ether (100 ml.) was added a solution of dihydroumbelliferone (3 g.) in ether (100 ml.) and the whole refluxed on the water-bath for 4 hr. Ether was distilled off as far as possible, thiophen-free benzene (100 ml.) added, and the mixture refluxed for another 4 hr. It was decomposed with ice–water and dilute sulphuric acid, the organic layer was separated, and the residue obtained on evaporation of the solvent was heated with 25% sulphuric acid (250 ml.) for 30 min. and then steam-distilled. 7-Hydroxy-2,2-dimethylchroman (VI) was obtained from the distillate (1·6 g., 50%) with b. p. 160°/8 mm., m. p. 70° (Found: C, 73·8; H, 8·2. Calc. for $C_{11}H_{14}O_2$: C, 74·2; H, 7·9%).

2,4-*Dimethoxybenzyl* 7-*Hydroxy*-2,2-*dimethylchroman*-6-*yl Ketone* (VII).—A mixture of 7-hydroxy-2,2-dimethylchroman (4·6 g.), 2,4-dimethoxybenzyl cyanide (5·2 g.), zinc chloride (1·5 g.), and dry ether (50 ml.) was saturated with hydrogen chloride at 0°, and then kept in the refrigerator for 3 days. The dark red solution was diluted with ether (150 ml.), a brown gum separating. Ether was decanted and the residue heated with water (200 ml.) and concentrated hydrochloric acid (10 ml.) for 2 hr. The resultant semisolid mass was taken up in ether, washed with water, dried (Na_2SO_4), and evaporated. The residual gummy *ketone* crystallised from aqueous ethanol in white plates (2 g.), m. p. 145° (Found: C, 70·4; H, 7·0. $C_{21}H_{24}O_5$ requires C, 70·8; H, 6·7%).

3-(2,4-*Dimethoxyphenyl*)-4′,5′-*dihydro*-4-*hydroxy*-6′,6′-*dimethylpyrano*[3′,2′:6,7]*coumarin* (VIII).—The preceding ketone (0·6 g.), ethyl chloroformate (0·7 ml.), anhydrous potassium

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[14] Langley and Adams, *J. Amer. Chem. Soc.*, 1922, **44**, 2320.

[15] Livshifts, Bazilevskaya, Bainova, Dobrovinskaya, and Preobrazhensku, *J. Gen. Chem.* (*U.S.S.R.*), 1947, **17**, 1671.

[16] Linstead and Thomas, *J.*, 1940, 1127.

carbonate (3 g.), and dry acetone (20 ml.) were refluxed on the water-bath for 5 hr. The cooled mixture was diluted with water (50 ml.) and acidified with concentrated hydrochloric acid. The solid precipitate was collected and warmed with N-sodium hydroxide (50 ml.) on a water-bath for 1 hr. Acidification of the alkaline solution afforded the 4-*hydroxycoumarin* (VIII) as a gelatinous precipitate (0·5 g.), m. p. 216—223°. This crystallised from ethanol in nodules, m. p. 230° (Found: C, 68·7; H, 6·1. $C_{22}H_{22}O_6$ requires C, 69·1; H, 5·8%). It gave an intense violet colour with alcoholic ferric chloride.

Isopsoralidin (III; R = H).—The 4-hydroxycoumarin (VIII) (0·5 g.) was heated with aniline hydrochloride (1·5 g.) at 210—220° for 3 hr. under carbon dioxide. The brown mass was leached with water and repeatedly extracted with ether. The crude phenolic product obtained on evaporation of the extracts was heated with methyl iodide (5 ml.) and anhydrous potassium carbonate (3 g.) in acetone (16 ml.) on a water-bath for 8 hr. Isopsoralidin monomethyl ether (III; R = Me), worked up in the usual way, was passed in benzene through an alumina column and then crystallised from benzene–light petroleum in colourless plates (60 mg.), double m. p. 174—175° and 198—200° (Found: C, 71·8; H, 5·2. Calc. for $C_{21}H_{18}O_5$: C, 72·0; H, 5·2%), $\lambda_{max.}$ 211, 245, 307, and 348 mμ (ε 42,000, 23,200, 9114, and 31,500, respectively). The mixed m. p. with authentic isopsoralidin methyl ether [2] was not depressed. The methyl ether (III; R = Me) (40 mg.) was demethylated with aniline hydrochloride as described above and the product sublimed, to give crystals (25 mg.), m. p. 280—283°. These were recrystallised twice from aqueous methanol, forming prisms, m. p. and mixed m. p.[2] 284—287° (Found: C, 71·1; H, 5·1. Calc. for $C_{20}H_{16}O_5$: C, 71·4; H, 4·8%), $\lambda_{max.}$ 245, 308, and 350 mμ (ε 19,600, 7223, and 24,960). The *monoacetate* (III; R = Ac), prepared by heating isopsoralidin (10 mg.) with acetic anhydride (0·5 ml.) and sodium acetate for 5 min., crystallised from ethanol in needles, m. p. 220° (Found: C, 69·4; H, 5·1. $C_{22}H_{18}O_6$ requires C, 69·8; H, 4·8%). The acetate prepared from natural isopsoralidin had the same m. p. and mixed m. p.

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